

Building Congested Ketone: Substituted Hantzsch Ester and Nitrile as Alkylation Reagents in Photoredox Catalysis

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S Supporting Information

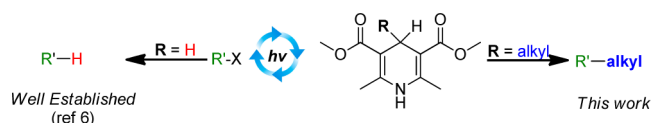
ABSTRACT: For the first time, 4-alkyl Hantzsch esters were used to construct molecules with all-carbon quaternary centers by visible light-induced photoredox catalysis via transfer alkylation. Up to a 1500 h⁻¹ turnover frequency was achieved in this reaction. Reactions of 4-alkyl Hantzsch nitriles as tertiary radical donors joined two contiguous all-carbon quaternary centers intermolecularly, and this chemistry was used to synthesize a common precursor of a class of hydroxysteroid dehydrogenase inhibitors.

Constructing all-carbon quaternary centers is a challenging synthetic task.¹ Intermolecular formation of bonds joining two contiguous all-carbon quaternary centers is even more difficult owing to thermodynamic disadvantages, and the number of strategies to construct these sterically congested structures is limited.² Visible light-induced photoredox catalysis has recently demonstrated potential for synthesis of novel molecules via highly reactive radicals.³ Various congested all-carbon quaternary centers have been constructed via photoredox strategies.⁴ However, intermolecular construction of two contiguous all-carbon quaternary centers by visible light-induced photoredox catalysis has not been reported.

The Hantzsch ester serves as a reductant in transfer hydrogenation reactions catalyzed by Brønsted and Lewis acids and transition metals.⁵ In addition, it acts as an electron and hydrogen donor in reactions involving cleavage of C–heteroatom bonds;⁶ reduction of azide compounds;⁷ and reductive coupling of imines and ketones.⁸ In processes other than the transfer hydrogenation reaction,⁹ Hantzsch ester homologues such as **2** have been known for more than 50 years¹⁰ but had not found any synthetic applications until recently.¹¹ For the only two examples, the Tang group reported Lewis acid catalyzed alkyl transfer reactions of alkyl Hantzsch esters, as well as AIBN-initiated radical substitution reactions. The excellent redox chemistry with the Hantzsch ester did not give rise to any advance for its substituted analogue. Herein, we report the use of alkyl Hantzsch esters for intermolecular construction of single all-carbon quaternary centers, as well as two contiguous centers, via visible light-induced catalytic alkyl transfer reactions (Scheme 1).

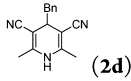
We began by optimizing the conditions for the alkyl transfer reaction of α -bromo-isobutyrophenone **1a** and 4-benzyl

Scheme 1. Hantzsch Ester in Photoredox Catalysis



Hantzsch esters **2a–2c** in the presence of Cs₂CO₃ and photocatalysts (Table 1). To our delight, Hantzsch ester **2a** gave a moderate yield of the desired product **3a** along with an 18% yield of isobutyrophenone from a transfer hydrogenation reaction. This selectivity was also observed in the reaction of **2b**. By introducing a *t*-Bu ester, we achieved a 91% yield with **2c** with

Table 1. Selected Results of Reaction Optimization Experiments^a

Entry	R	Catalyst	Yield (%) ^[b]
1	Me (2a)	<i>fac</i> -Ir(ppy) ₃	44 ^[c]
2	Et (2b)	<i>fac</i> -Ir(ppy) ₃	40
3	<i>t</i> -Bu (2c)	<i>fac</i> -Ir(ppy) ₃	91 ^[d]
4	<i>t</i> -Bu (2c)	<i>fac</i> -Ir(ppy) ₃	89 ^[d,e]
5	<i>t</i> -Bu (2c)	<i>fac</i> -Ir(ppy) ₃	44 ^[d,f]
6	<i>t</i> -Bu (2c)	Ir(ppy) ₂ (dtbpy)PF ₆	87 ^[d]
7	<i>t</i> -Bu (2c)	Ru(byp) ₃ Cl ₂	NR
8	 (2d)	<i>fac</i> -Ir(ppy) ₃	41

^aConditions: **1a** (0.1 mmol), **2** (0.3 mmol), Cs₂CO₃ (0.1 mmol), CH₃CN, 1 mol % catalyst, 12 W white LEDs, 40 min, rt. ^bUnless otherwise noted, yields were calculated by GC with diphenylketone as an internal standard. NR = no reaction. ^cIsobutyrophenone was obtained in 18% yield. ^dIsolated yield. ^e0.1 mol % catalyst loading. ^f0.01 mol % catalyst loading.

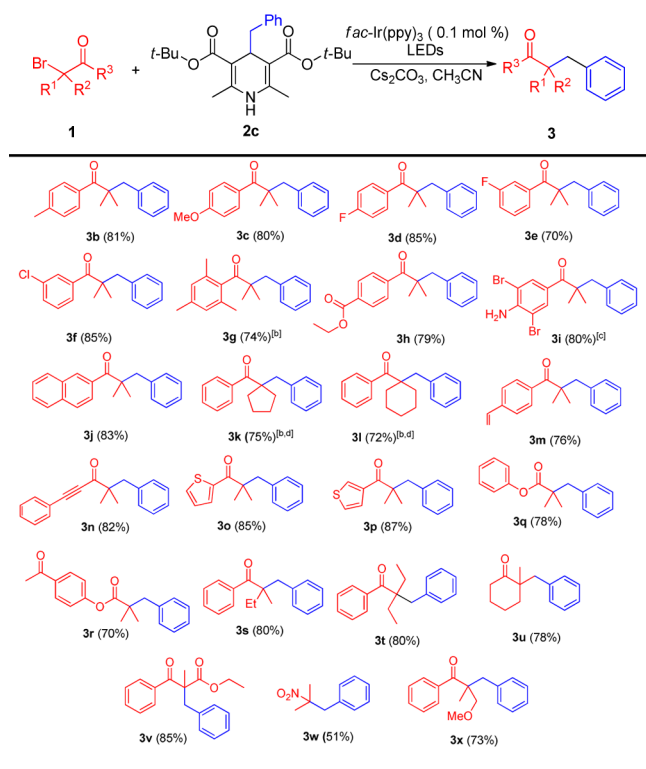
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1 mol % *fac*-Ir(ppy)₃. With 0.1 mol % *fac*-Ir(ppy)₃ as the photocatalyst and Cs₂CO₃ as the base, the reaction of **2c** was complete in 40 min with a turnover frequency up to 1500 h⁻¹ with almost the same yield as that from a 1.0 mol % catalyst loading. A further decrease in the catalyst loading resulted in decreased yield (entry 5). When Ir(ppy)₂(dtbpy)PF₆ was used instead, the reaction gave a similar yield (entry 6). There was no product detected when a ruthenium catalyst was used (entry 7). When the Hantzsch nitrile **2d** was used instead, low conversion was observed due to the reduced reactivity of **2d** (entry 8).

Using the optimized conditions (Table 1, entry 4), we screened various substrates **1** in reactions with Hantzsch ester **2c** as the alkyl donor (Table 2). To our delight, a broad range of

Table 2. Visible Light-Induced Alkyl Transfer Reactions of Hantzsch Ester **2c with Compounds **1**^a**

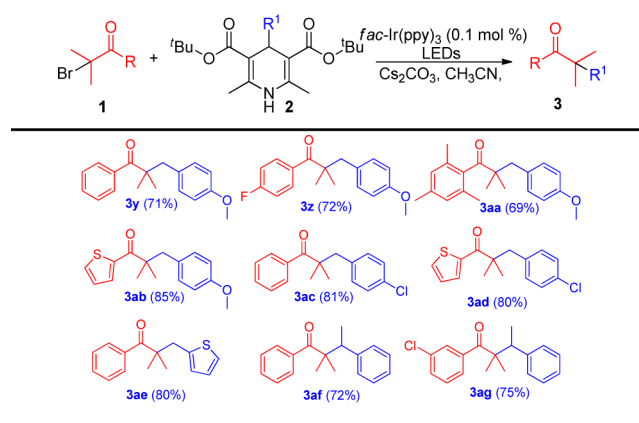


^aConditions: **1** (0.1 mmol), **2c** (0.3 mmol), *fac*-Ir(ppy)₃ (0.1 mol %), Cs₂CO₃ (0.1 mmol), CH₃CN (2.0 mL), 12 W white LEDs, rt, 1 h, isolated yields. ^b0.2 mol % *fac*-Ir(ppy)₃. ^c0.3 mol % *fac*-Ir(ppy)₃. ^dReaction time 2 h.

functional groups were tolerated, and we obtained good yields of desired products **3b–3l**, including ring-containing products **3k** and **3l**. Substrates **1m** and **1n** did not undergo any detectable radical addition reactions of the alkene or alkyne substituent and yielded **3m** and **3n** as the only adducts. Thiophene-containing substrates **1o** and **1p** gave the corresponding products (**3o** and **3p**) in high yields. In addition to the α -bromo ketones, α -bromo esters **1q** and **1r** were also converted to the corresponding products **3q** and **3r** in good yields. Compounds **3s** and **3t** with Me/Et and Et/Et substituents also gave good yields. Cyclic ketone **3u** and keto-ester **3v** were also obtained in good yields. 2-Bromo-2-nitropropane was also compatible with this protocol, and desired product **3w** was achieved in moderate yield. Compound **3x** with a methoxyl could be prepared in 73% yield.

Next, we used a series of 4-alkyl Hantzsch esters **2** to construct products with all-carbon quaternary centers by reaction with **1** (Table 3). Hantzsch esters **2e** with an electron-donating

Table 3. Scope of Alkyl Transfer Reactions of Hantzsch Esters **2^a**



^aConditions: **1** (0.1 mmol), **2** (0.3 mmol), *fac*-Ir(ppy)₃ (0.1 mol %), Cs₂CO₃ (0.1 mmol), CH₃CN (2.0 mL), 12 W white LEDs, rt, 1 h, isolated yields.

methoxy group and **2f** with an electron-withdrawing chloride atom were suitable for C–C bond formation (affording products **3y–3ad**). An ester **2g** with a thiophenylmethyl substituent gave heterocyclic product **3ae** in good yield. To our delight, the Hantzsch ester **2h** could even donate a tertiary benzyl moiety to generate sterically congested compounds **3af** and **3ag** with reactivity comparable to the reactivities of less-hindered esters.

In order to gain some insight into the reaction, we performed control experiments and calculations. First, we confirmed that the reaction did not proceed in the absence of either light or *fac*-Ir(ppy)₃; the electron-donor–acceptor complex was not observed by NMR or UV–vis spectroscopy. A Stern–Volmer plot showed strong quenching of *fac*-Ir(ppy)₃ ($E_{1/2}^{*\text{III/II}} = +0.31$ V vs SCE) by Hantzsch ester **2c** ($E_{1/2}^{\text{red}} = +1.08$ V vs SCE), favoring a reductive quenching cycle (Figure 1).¹²

Hantzsch esters **2a–2c** are similar in terms of electrochemistry and spectroscopy, but reacted distinctly in the reaction (Table 1, entries 1–3). So a density functional theory calculation on the pathways of C–C bond cleavage that provide the coupling unit was carried out at the B3LYP/6-311G(d,p) level (Scheme 2a).

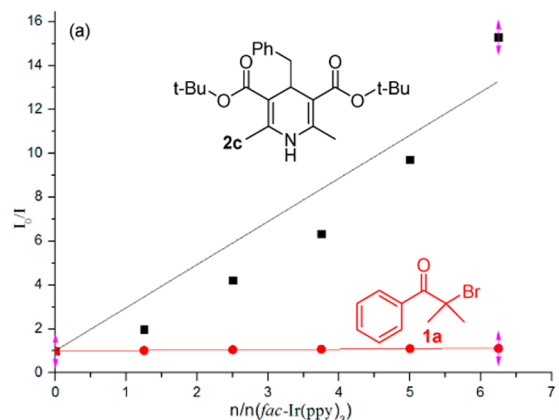
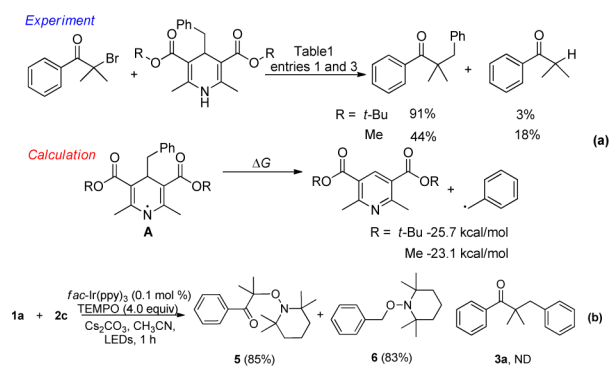


Figure 1. Fluorescence quenching of *fac*-Ir(ppy)₃ by **2c** or **1a**.

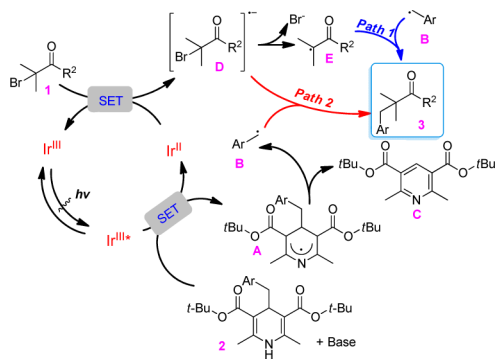
Scheme 2. Radical Generated from Different Ester and Radical-Capturing Reaction



The difference of free energy (ΔG) for the reaction from the radicals **A** to the benzyl radical and corresponding pyridine suggested the *t*-Bu Hantzsch ester radical intended to expel the side benzyl group to form the less-congested pyridine compounds. This difference might account for the predominant C–C bond formation in the case of **2c**. In order to investigate the radical species in the reaction, a standard reaction (Table 1, entry 4) was carried out in the presence of 4.0 equiv of TEMPO (Scheme 2b). Two TEMPO derivatives **5**¹³ and **6**¹⁴ could be isolated in comparable yield above 80%, and **3a** was not generated.

A plausible pathway is proposed in Scheme 3. The reaction starts with the oxidation of **2** by the excited-state *fac*-Ir(ppy)₃* in

Scheme 3. Plausible Reaction Mechanism

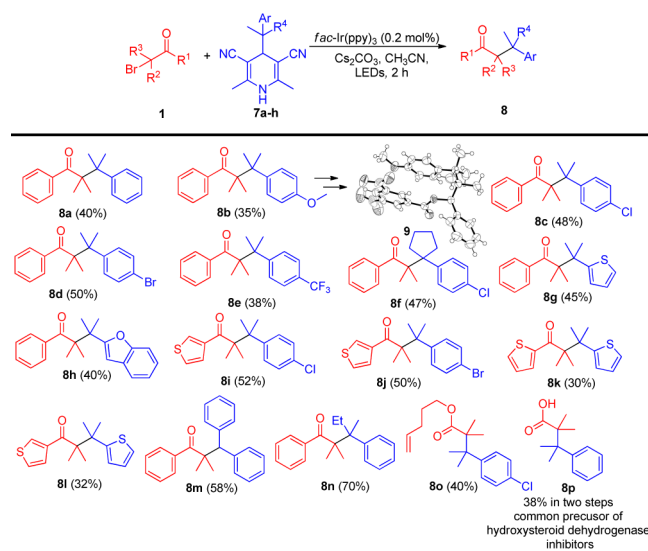


the presence of base, yielding radical **A** and Ir^{II}. Cleavage of the C–C bond, driven by aromatization of **A**,¹⁵ affords benzyl radical **B** (Ar = Ph, $E_{1/2}^{\text{red}} = -1.43$ V vs SCE)¹⁶ and byproduct pyridine **C**. The Ir^{II} species ($E_{1/2}^{\text{III/II}} = -2.19$ V vs SCE) effects second single electron transfer (SET) to compound **1** ($E_{1/2}^{\text{red}} = -1.65$ V vs SCE), giving the anionic radical **D**, which undergoes mesolysis to radical **E** and bromide.¹⁷ The coupling of **E** and benzyl radical **B** generates the product **3** (path 1).¹⁸ Another pathway **2** that includes direct coupling between anionic radical **D** and radical **B** is also possible from the computational study (Supporting Information, part 16.2). Meanwhile, an iridium species might work as a catalyst in the process of C–C bond formation.¹⁹ Note that other pathways are also possible for further investigation.

With the results achieved with the benzyl Hantzsch ester, we further hypothesized that strong steric hindrance could be overcome during the formation of the new C–C bond. Therefore, we explored the possibility of connecting two all-carbon quaternary centers by means of an intermolecular

reaction. We were unable to prepare a Hantzsch ester with an all-carbon quaternary side chain, so we instead prepared a series of Hantzsch nitriles substituted with an all-carbon quaternary center and subjected the nitriles to the protocol with various substrates **1**. (Table 4) To our delight, congested ketone **8a** was

Table 4. Joining of Two All-Carbon Quaternary Centers with Hantzsch Nitriles^a



^aConditions: **1** (0.2 mmol), **7** (0.6 mmol), *fac*-Ir(ppy)₃ (0.2 mol %), Cs₂CO₃ (0.2 mmol), CH₃CN (4.0 mL), 12 W white LEDs, rt, 2 h. Isolated yield after chromatography.

the major product of the reaction of **1a** and **7a**. To our knowledge, this is the first report of the joining of two all-carbon quaternary centers by means of visible light-induced photoredox catalysis. We confirmed the structure of products **8** by converting **8b** to corresponding 3,5-dinitrobenzoate **9** and subjecting it to X-ray diffraction analysis. In addition to tetramethyl products **8c**–**8e**, we could obtain **8f**, which has two methyl groups and a cyclopentyl group, after irradiation of the corresponding substrates with 12 W white LEDs for 2 h in the presence of 0.2 mol % *fac*-Ir(ppy)₃. Nitriles and bromoketones with heterocyclic groups such as thiophene and benzofuran were evaluated and gave heterocycle–phenyl, phenyl–heterocycle, and heterocycle–heterocycle product combinations (**8g**–**8l**). The moderate yields of the reactions with **7** might be due to its high oxidative potential relative to that of **2**, which made the electron transfer cycle involving **7**²⁰ less effective than that involving **2**. This difference led to side reactions such as hydrolysis and elimination of **1**. An exception was that compound **8n** with even more congested carbon centers was prepared in 70% yield. Ester **8o** was achieved with the same protocol in 40% yield, and carboxylic acid **8p**, a common precursor for a class of hydroxysteroid dehydrogenase inhibitors,²¹ was prepared in 38% yield in two steps.

In summary, we report the first use of alkyl transfer reactions involving 4-alkyl Hantzsch esters and their nitrile analogues to construct products with a single all-carbon quaternary center, or with two contiguous centers, via visible light-induced photoredox catalysis. A turnover frequency up to 1500 h^{−1} was achieved with a 0.1 mol % catalyst loading.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06379.

Crystallographic data (CIF)

Experimental procedures, compound characterizations, spectra, GC traces, and calculation details (PDF)

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Notes

The authors declare no competing financial interest.

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